



## Fosfomycin Tromethamine (Monurol®)

**Classification:** Antibiotic

### Pharmacology:

MONUROL (fosfomycin tromethamine) Granules for Oral Solution contains fosfomycin tromethamine, a broad spectrum bactericidal antibiotic. Fosfomycin (the active component of fosfomycin tromethamine) has in vitro activity against a broad range of gram-positive and gram-negative aerobic microorganisms which are associated with uncomplicated urinary tract infections. As a phosphonic acid derivative, fosfomycin inhibits bacterial wall synthesis by inactivating the enzyme, enolpyruvyl transferase, which is critical in the synthesis of cell walls by bacteria.<sup>1</sup>

### Pharmacokinetics:<sup>1</sup>

<b>Absorption</b>	<b>Following oral administration, fosfomycin tromethamine is rapidly absorbed and converted to the free acid, fosfomycin. After a single 3-gram dose of fosfomycin, the mean maximum serum concentration achieved was 26.1 mcg/mL within 2 hours; with a high-fat meal it was 17.6 mcg/mL within 4 hours.</b>
<b>Distribution</b>	Fosfomycin is distributed to the kidneys, bladder wall, prostate, and seminal vesicles. Fosfomycin is not protein bound. The mean apparent steady-state volume of distribution is 136.1 L.
<b>Elimination</b>	Fosfomycin is excreted unchanged in urine (38%) and feces (18%). Mean half-life elimination is 5.7 hours; CrCl 7-54 mL/min is 50 hours. Urinary excretion decreases to 11% in patients with CrCl 7-54 mL/min.

### Indications and Usage:

- Fosfomycin is FDA approved for the treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.<sup>1</sup>
- Off-label use in males for uncomplicated urinary tract infections and prostatitis.<sup>2</sup>
- Not indicated for the treatment of pyelonephritis or perinephric abscess.<sup>1</sup>
- If persistence or reappearance of bacteriuria occurs after treatment with fosfomycin, other therapeutic agents should be selected.<sup>1</sup>

### Dosage and Administration:

- The FDA approved dosage for females 18 years of age and older for uncomplicated urinary tract infection (acute cystitis) is 3 g (one sachet) of fosfomycin.<sup>1</sup>
- Off-label use in males for complicated urinary tract infection is 3 g every 2 to 3 days for 3 doses orally. The off-label use for prostatitis is 3 g every 3 days for a total of 21 days orally.<sup>2</sup>
- Fosfomycin may be taken with or without food.
- Always mix fosfomycin with 3 to 4 oz (90 to 120 mL) cool water before ingesting. Do not administer in its dry form or mix with hot water.

### **Contraindications:**

Fosfomycin is contraindicated in patients with known hypersensitivity to the drug.<sup>1</sup>

### **Precautions:<sup>1</sup>**

- Prolonged use may result in fungal or bacterial superinfection. *Clostridium difficile* associated diarrhea (CDAD) and pseudomembranous colitis has been reported with use of nearly all antibacterial agents, including fosfomycin, and may range in severity from mild diarrhea to fatal colitis. Therefore, careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
- Do not use more than one single dose of fosfomycin to treat a single episode of acute cystitis. Repeated daily dose increased the risk for adverse events.
- Reduced renal excretion in renal impairment (CrCl < 54 mL/min)
- Fosfomycin crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, fosfomycin should be used during pregnancy only if clearly needed.

### **Interactions:<sup>1-2</sup>**

- *Metoclopramide*: when coadministered with fosfomycin increases gastrointestinal motility, lowers the serum concentration and urinary excretion of fosfomycin. Other drugs that increase gastrointestinal motility (e.g. erythromycin) may produce similar effects.
- *Sodium Picosulfate*: antibiotics may diminish the therapeutic effect of sodium picosulfate. Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic.
- *Lactobacillus and Estriol*: antibiotics may diminish the therapeutic effect of lactobacillus and estriol.
- *BCG, Cholera and Typhoid vaccines (live attenuated Ty21a strain)*: Systemic antibiotics may diminish the therapeutic effect of vaccine.

### **Adverse Reactions:<sup>1-2</sup>**

In clinical trials, the most frequently reported adverse events occurring in >1% of the study population regardless of drug relationship were: diarrhea 10.4%, headache 10.3%, vaginitis 7.6%, nausea 5.2%, rhinitis 4.5%, back pain 3.0%,

dysmenorrhea 2.6%, pharyngitis 2.5%, dizziness 2.3%, abdominal pain 2.2%, pain 2.2%, dyspepsia 1.8%, asthenia 1.7%, and rash 1.4%.

### Cost Comparison:

Name	Treatment Duration (days)	Unit Cost	Total Cost
<b>Fosfomycin 3 gm once</b>	1	\$79.38	\$79.38
<b>Nitrofurantoin 100 mg twice daily</b>	5	\$0.95	\$9.50
<b>Sulfamethoxazole /trimethoprim 800/160 mg twice daily</b>	3	\$0.12	\$0.72

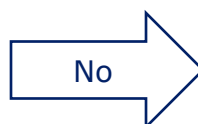
### Guidelines:

The CDC Antibiotic Prescribing and Use in Doctor's Offices Adult Treatment Recommendations report that nitrofurantoin, trimethoprim/sulfamethoxazole (where local resistance is < 20%) and fosfomycin are all appropriate first-line agents for the treatment of uncomplicated cystitis in health adult non-pregnant postmenopausal women. The CDC recommends that fluoroquinolones such as ciprofloxacin should be reserved for situations in which other agents are not appropriate.<sup>3</sup>

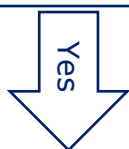
The International Clinical Practice Guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women also recommends nitrofurantoin 100 mg BID x 5 days, trimethoprim/sulfamethoxazole 160/800 mg (where local resistance is < 20%) BID x 3 days and fosfomycin 3 gm single dose as first-line empiric treatment options to consider (figure 1). If one of these agents cannot be used due to availability, allergy history, tolerance or resistance then use of a fluoroquinolone or  $\beta$ -lactam (not ampicillin or amoxicillin) may be considered.<sup>4</sup>

Woman with acute uncomplicated cystitis able to take oral medication

- Absence of fever, flank pain, or other suspicion for pyelonephritis

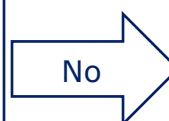


Consider alternate diagnosis



Can one of the recommended antimicrobials be used considering availability, allergies and tolerance?

- Nitrofurantoin
- Trimethoprim-sulfamethoxazole 160/800 mg (avoid if resistance exceeds 20% or if used in previous 3 months)
- Fosfomycin



Fluoroquinolone or  $\beta$ -lactam (avoid ampicillin or amoxicillin alone)

Figure 1: Algorithm for choosing empirical treatment of acute uncomplicated cystitis. Adapted from IDSA guidelines 2010.

### **Efficacy:**

Efficacy of fosfomycin tromethamine has been well documented when compared to nitrofurantoin, trimethoprim/sulfamethoxazole, and fluoroquinolones. Fosfomycin tromethamine has a broad spectrum of activity against gram-negative and gram-positive uropathogens, is bactericidal and shows no cross-resistance with other antibiotics because of its unique chemical structure. It results in high concentrations in the urine with a low excretion rate allowing for single-dose treatment in uncomplicated cystitis in women.

#### Fosfomycin vs. Nitrofurantoin

One study evaluated the efficacy and tolerability of fosfomycin trometamol (n=116) in a single dose of 3 gm compared to nitrofurantoin (n=115) in a dose of 50 mg four times daily for 7 days. In this study, the 9 day cure rate was 81% for fosfomycin and 90% for nitrofurantoin. However, the overall 42 day post-treatment cure rate was 85% for fosfomycin and 82% for nitrofurantoin. The relapse/reinfection rate was 11% for fosfomycin and 13% for nitrofurantoin. Statistically these differences were not significantly different. Fosfomycin treated patients reported more gastrointestinal side effects day 4 (fosfomycin 72% vs. nitrofurantoin 65%) and day 9 (fosfomycin 61% vs. nitrofurantoin 42%) of the study and symptoms were generally reported to be mild.<sup>5</sup>

Single-dose fosfomycin tromethamine (n=375) and multi-dose nitrofurantoin (n=374) were comparably efficacious in the treatment of uncomplicated UTI, in a randomized, multi-center, double-blind clinical trial. Women with uncomplicated UTI received either a 7 day regimen of twice daily nitrofurantoin 100 mg or a single-dose of fosfomycin 3 gm. Bacteriologic cure rates were similar for nitrofurantoin and fosfomycin at one week post-treatment (81% and 78%, respectively). Clinical cure rate was 80% for both drugs. There was no significant difference between groups with regard to re-infection rate, whereas fosfomycin treated patients experienced significantly fewer relapses compared with the nitrofurantoin treatment group. Adverse events were similar among the 2 groups, and were mild in severity.<sup>6</sup>

Pregnant patients attending antenatal clinics found to have significant bacteriuria without presenting UTI symptoms were evaluated. Patients were randomly allocated to receive either a single dose of fosfomycin trometamol one 3 gm sachet or nitrofurantoin 100 mg twice daily for 7 days. Bacteriological efficacy in 23 subjects were evaluated 15 days after therapy and then monthly until birth. Treatment response (cure) was reported to be similar for both groups, 84% with fosfomycin and 90% with nitrofurantoin. No adverse effects were reported with

fosfomycin and 2 patients treated with nitrofurantoin reported adverse effects, one had nausea and the other nausea and vomiting.<sup>7</sup>

#### Fosfomycin vs. trimethoprim/sulfamethoxazole

Fosfomycin tromethamine (3 grams orally as a single dose) was found to be at least as effective as trimethoprim/sulfamethoxazole 960 milligrams orally daily for 3 days in uncomplicated urinary tract infections in one small study. In larger study, single oral doses of fosfomycin tromethamine (3 grams) and trimethoprim/sulfamethoxazole (1.92 grams) were similarly effective in treating female uncomplicated urinary tract infections. In both studies, the overall incidence and severity of adverse effects were similar with each agent, although diarrhea was observed more often with fosfomycin.<sup>8</sup>

Another study evaluated single dose fosfomycin trometamol 3 gm (n=224), co-trimoxazole (trimethoprim/sulfamethoxazole) 1.92 gm (n=109) and ofloxacin 200 mg (n=113) in female patients with acute uncomplicated UTI. Follow-up examinations occurred after one and four weeks in order to check for clinical and bacteriological success of therapy. At one week urine samples were sterile in 68.7%, 71% and 85.4% of fosfomycin, co-trimoxazole and ofloxacin treated patients with prior significant bacteriuria. At four weeks urine samples with nonsignificant pathogen counts were 81.9%, 79.4% and 80.8% of fosfomycin, co-trimoxazole and ofloxacin treated patients with prior significant bacteriuria. At four weeks persistent bacteriuria was present in 4.7%, 6.3% and 9% of fosfomycin, co-trimoxazole and ofloxacin treated patients. Gastrointestinal symptoms were the most commonly reported side effects and were similar among the treatment groups.<sup>9</sup>

In a randomized, comparative study in women with uncomplicated urinary tract infections, a single 3 gram dose of fosfomycin tromethamine was as effective as a 5-day course of ciprofloxacin. Women aged 18 to 65 years with uncomplicated urinary tract infections were randomized to receive either a single 3 gram oral dose of fosfomycin or ciprofloxacin 500 mg orally twice daily for 5 days. Primary efficacy outcomes were clinical response and bacteriological cure at follow-up. *Escherichia coli* and *Enterobacter* species were the most commonly isolated bacterial pathogens. For *E coli*, sensitivity was 94% and 59% for fosfomycin and ciprofloxacin. For *Enterobacter*, sensitivity was 75% and 85%, respectively. Bacteriological cure occurred in 83.1% in fosfomycin group and 78.4% for ciprofloxacin.<sup>10</sup>

#### **Conclusions:**

Fosfomycin has been shown to be effective in multiple studies with tolerability generally comparable to other antibiotics used in the treatment of UTI. Several trials have shown the efficacy of fosfomycin is similar to nitrofurantoin, trimethoprim/sulfamethoxazole and fluoroquinolone antibiotics such as ofloxacin

and ciprofloxacin. Fosfomycin can be an appealing therapeutic option to treat uncomplicated UTI because it is a single-dose regimen and has few clinically relevant drug interactions. This antibiotic has relatively low use and an unshared mechanism of action with other antibiotics coupled with a low resistance rate. Fosfomycin is used to treat uncomplicated UTIs because of its broad spectrum of activity including resistant other pathogens associated with UTIs. However, compared to other first-line empiric antibiotic treatments, fosfomycin is more expensive than the other options.

**Recommendation:**

Consider the addition of fosfomycin to the formulary as it may be a beneficial empiric treatment option for uncomplicated UTI, particularly for those facilities with high trimethoprim/sulfamethoxazole resistance (>20%).

**References:**

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